QbD BASED ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR THE ESTIMATION OF FEW DRUGS IN BULK AND IN THEIR DOSAGE FORM

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1. ABSTRACT

Pharmaceutical analysis plays a very vital role in quality assurance as well as quality control of bulk drugs and pharmaceutical formulations. Rapid increase in pharmaceutical industries and production of drug in various parts of the world has brought an increase in demand for new analytical techniques in the pharmaceutical industries. Drug analysis plays an important role in the development of drugs, their manufacture and therapeutic use. Recent development in analytical methods has been resulted from the advancement of analytical instruments. The improvement of the analytical method development and analytical instruments have reduced the time of analysis, increased precision and accuracy and reduced costs of analysis. Quality by design (QbD) is a systematic approach to product or process development, which begins with predefined objectives, uses science and risk management approach to gain product or process understanding and ultimately process control. The process of QbD can be applied to analytical methods. This research proposal involves systematic development of a simple, fast, sensitive, reproducible and cost effective analytical QbD method, applying the principles of QbD for quantification of selected drugs.

2. INTRODUCTION

Pharmaceutical analysis is the application of principles of analytical chemistry to drug analysis. It plays a very significant role in quality control of pharmaceuticals through a rigid check on raw materials used in manufacturing of formulations and on finished products. It also plays an important role in building up the quality products through in process quality control. It also plays a major role in isolation and characterization of impurities. The key requisite for success in this field is a thorough knowledge of various fields of chemistry and excellent interactions with the experts of various other disciplines[1].

Analytical testing is one of the important aspects of pharmaceutical development. Having the right analytical method is vital in ensuring the quality of the drugs. Various analytical techniques are used to test the physical, chemical, and biological parameters of the subjected pharmaceutical product. Chromatographic techniques (HPLC, UHPLC, etc.) are the most widely used techniques in the pharmaceutical industry due to its advantages over the other techniques[2].

Development in scientific and concrete analytical methods has been resulted from the advancements of analytical instruments. The improvements of the analytical method development and analytical instruments have reduced the time and cost of analysis and enhanced precision and accuracy. Techniques pertaining to analysis are developed and validated for active pharmaceutical ingredients, excipients, related substances, drug products, degradation products and, residual solvents, etc. resulting which become an integral part of the required necessities for regulatory organization[3].

Analytical method development finally results in official test methods. Consequently quality control laboratories used these methods to check the efficacy, identity, purity, safety as well as performance of products of the drug. Regulatory authorities give utmost importance on analytical methods in manufacturing. Drug approval by regulatory authorities requires the applicant to prove control of the entire process of drug development by using validated analytical methods[3].

Development of a specific and robust stability-indicating LC method for the determination of related substances and degradation products is a complex process. It requires a deliberate forced degradation of a drug substance and/or a drug product under various stress

conditions, such as hydrolytic, oxidative, photolytic, or thermal conditions, to provide stressed samples containing the analyte and its degradation products. The stress conditions are more severe than the accelerated and long-term stability conditions prescribed in the ICH guidelines for stability testing. Analytical method for determination of degradation products should be capable of detecting their increase during the product's shelf life, and the method for the assay should be capable of detecting any decrease in the drug substance's content during its shelf life. Such methods are stabilityindicating[4].

Analytical Method Development:

Method development usually requires selecting the method requirements and deciding on what type of instrumentation to utilize and why to utilize. The development of any new or improved method usually tailors existing approaches and instrumentation to the current analyte as well as to the final needs or requirements of it.

Need for Analytical Method Development:

- Any official method is not reported in IP, BP and USP for estimation of drug or combination of drugs.
- Due to patent regulations, a systemic analytical method may not be available for the drug and drug combinations in the literature
- Analytical methods may not be available for the drug in the form of a formulation due to the interference caused by the formulation excipient.
- Analytical methods for the quantitation of the drug may not be available.
- Reported analytical procedures may require expensive reagents and solvents. It may also involve cumbersome extraction and separation procedures and these may not be reliable[1,5,6].

ANALYTICAL METHOD VALIDATION

Principle purpose of the method validation is to ensure that a selected analytical method will give reproducible and reliable results that are adequate for the intended purpose. Validation of analytical method is to be done according to ICH guidelines.

Various validation parameters are; accuracy, precision (repeatability, intermediate precision and reproducibility), linearity and range, limit of detection (LOD)/ limit of quantitation (LOQ), robustness, specificity[7,8].

Analytical Quality-by-Design

A Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management[9].

The field of AQbD is likely to progress in the pharmaceutical industry, as positive results have already been realized from its wide implementation. The analytical methods, most of them were based on one factor at a time (OFAT), wherein one constraint alone is optimized for the response while others were kept constant. This routine yields a narrow robust behavior of the method. Therefore the usually followed strategy of analytical method (i.e., OFAT) development has high risk in method failure and requires a revalidation program to be commenced then and there. The AQbD application in method developments that were published to date stresses the organized development of a method through unassailable decision-making obtained from surveying and evaluation of methods. And also the most imperative benefits include that these AQbD methods are more rugged and robust, and that endure the contests of long-term usage by analytical laboratories with a reduced chance of failure were able to be developed. More knowledge has been gained during the complex method development with advanced techniques (such as UPLC, HPTLC-MS) using AQbD because AQbD applied method shall meet critical quality attributes that was laid down before the start of the development of the method. Since multiple responses needs to be optimized desirability function helps to achieve the same The development of AQbD thrives on the support by pharma-industry and the researcher's own interest. Hence encouragement to implement the response surface methodology combined with desirability function helps the analytical chemist's to ride over the entire difficult situation faced in production of a quality and efficacy products. (Formulation or batch release after manufacturing)[16].

Table 1: Difference between AQbD and conventional method development.

Parameter	**Conventional Strategy**	**AQbD**
Approach	Factual	Systematic
Assurance of quality	End testing	Built in to a method
Specification	Previous knowledge	Analytical Product profile
Regulatory flexibility	Fixed cannot modify	Flexible within operable design region
Issues	Out of trend or control	No such issues
Benefit	Limited	No revalidation, robust

3. REVIEW OF LITERATURE AND DEVELOPMENT IN THE SUBJECT

The concept of Quality by Design (QbD) was introduced by Juran. Quality by design refers to the product or service development process in the organization[15]. QbD describes a pharmaceutical development approach referring to formulation design and development and manufacturing processes to maintain the prescribed product quality[9,10,11,12].

According to applications the analytical methods can be broadly divided in to three levels as follows.[16]

1) Process analytical Techniques –

- Provide real time information (at-, on- and in-line testing) for process control and improvement
- Non-traditional analytical techniques have been used in these areas: identification, drying, blending, assay, and content uniformity

2) Analytical methods for routine analysis

- Provides data for tracking and trending
- Quantitative results are more useful than PASS/FAIL
- Traditional analytical techniques, e.g. HPLC, Dissolution testing, are used.

3) Analytical methods for non-routine analysis –

Evaluation of product quality on periodic basis for higher quality assurance Reassessment of process or product upon process changes can use non-traditional analytical techniques that are not typically applied to routine release testing.

Lifecycle of an analytical method, under QbD paradigm, is shown in figure below[17].

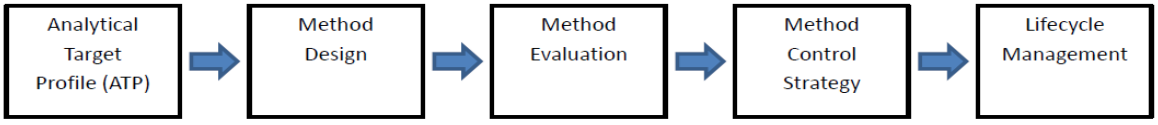

Figure: 1. Analytical method development with QbD approach

Process Analytical Technology (PAT):

A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

Analytical Target Profile:

The ATP is a tool that can be used in the establishment of any analytical methodology, whether intended as a component of a QbD approach or in the development approaches that have been used historically. In either case, the ATP can be used to describe the method requirements needed to adequately measure the defined CQAs of the drug product. An ATP would be developed for each method used in the overall product control strategy; it would define what the method has to measure and to what level the measurement is required (i.e., performance level characteristics—such as precision, accuracy, working range, sensitivity—and the associated performance criteria). It is this ATP that would drive the design and development of appropriate analytical methods and it is proposed that the ATP could also form the basis of a regulatory submission.

Critical Process Parameter (CPP):

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Critical Quality Attribute (CQA):

A physical, chemical, biological or microbiological property or characteristic thatshould be within an appropriate limit, range, or distribution to ensure the desired product quality.

Method Design:

Once the method requirements are thoroughly understood and the ATP is defined, an appropriate analytical method can be designed to achieve the desired measurement of the material, process, or product attribute. Information to be considered during the analytical-method design phase might include: prior experience with similar measurements or matrices, regional or geographic limitations and/or availability of reagents, supplies, or specific technologies in

laboratories that will be conducting the testing and cycle-time requirements to support process operations. Having identified a suitable analytical method, the factors that can influence the performance of an analytical method can be mapped against the unit operations within the method. The method design phase then continues by systematically evaluating the impact of each factor.

This assessment can be performed either through the utilization of appropriate risk assessment tools or based on experience (prior knowledge) or a combination of both.

Method Evaluation:

The next step is the method evaluation phase where the factors that have been identified as having a potential impact on method performance are evaluated (e.g., through structured multivariate design-of-experiment investigations or appropriate screening experiments). A preliminary assessment of the potential impact of the factors may also be explored using a robustness screening design (e.g., a Plackett-Burman fractional factorial experiment).

Method Control Strategy:

The outcome of method evaluation phase leads to final definition of the operating parameters and parameter ranges required to ensure performance of the analytical method. These set points and operating ranges are specified and a change-control process is implemented to ensure control of the established method parameters. It is imperative to reach a high degree of confidence that the analytical method will meet all method performance criteria under all conditions of use as it progresses through the lifecycle. This confidence level can be achieved by using a rigorous approach for identifying all the potential method factors that may need to be controlled to ensure method performance and through the use of risk assessment tools and prioritized experimentation that eliminate areas of risk.

Risk assessment:

A cause-and-effect diagram, also known as a fishbone or Ishikawa diagram, can then be used after the walk through to facilitate brainstorming of all the potential factors that may influence the method performance criteria.

Method robustness:

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage (ICH Q2 Validation of Analytical Procedures: Text and Methodology). The definition of robustness using a QbD approach adapted from the guideline would be: The robustness of an analytical method is defined as the capacity of its analytical method performance characteristics to remain unaffected by small variations in analytical method parameters that the method is likely to encounter under normal conditions of use.

Method ruggedness:

The ruggedness of an analytical method is the degree of reproducibility of test results obtained by the analysis of the same sample under a variety of normal test conditions such as different laboratories, different analysts, different instruments, different lots of reagents, different elapsed assay times, different assay temperatures, different days, and so forth (i.e, US Pharmacopeia). The definition of ruggedness using a QbD approach would then be: The ruggedness of an analytical method is defined as the capacity of a method to remain unaffected by variations due to noise factors that the method is likely to encounter under normal conditions. Ruggedness may be assessed through structured experimentation such as intermediate precision studies[9,10,17].

4. AIM, OBJECTIVE AND RATIONAL OF RESEARCH WORK

Aim of the present work is to develop a new, simple, robust, accurate, precise, economic validated analytical methods. The optimization phase will be done by using QbD.

The primary objective of proposed research work is as follows:

1. Selection and procurement of drug combinations and APIs for analysis.

2. To develop a simple, economic, accurate, rapid and reproducible analytical methods by using chromatographic techniques.

3. To implement QbD approach by using DoE technique to measure the effect of critical factors.

4. Identification of and Optimization of the chromatographic factors that had significant effects on separation attributes.

5. To validate the performance of the optimized methods as per ICH guidelines.

6. To apply stress condition as per ICH guidelines.

7. Statistical analysis of developed analytical methods.

RATIONAL OF RESEARCH WORK:

The number of new drugs introduced into the market every year. These drugs may be either new entities or partial structural modification of the existing one. Very often there is a time delay from the date of introduction of a drug into the market to the date of its inclusion in pharmacopoeias. This happens because of the possible uncertainties in the continuous and wider usage of these drugs, reports of new toxicities (resulting in their withdrawal from the market), development of long-suffering opposition and introduction of better drugs by competitors. Under these conditions, standards and analytical procedures for these drugs may not be available in the pharmacopoeias. It becomes necessary, therefore to develop newer analytical methods for such drugs.

Quality has been given an importance by all regulatory bodies for pharmaceutical products. Quality means customer satisfaction in terms of service, product, and process. Many of these quality related activities reflect need for companies to excel in global competition. Quality, productivity, cost, cycle time and value are interrelated terms. Quality activities must try to detect quality problems early enough to permit actions without requiring compromise in cost, schedule or quality. The emphasis must be on precaution rather than on just correction of quality problems. Quality can be the driving force to empower results in other parameters. Hence the quality has to be built in the product as well as services through proper planning, so that the forth coming failure can be avoided. Mere analysis of final product will not work but the quality should be designed in the product.

The principles of QbD have been used to advance the product and process quality in every industry. Because of need of potent drug with safety profile, pharmaceutical industries are investing billions of money in the drug discovery and development process with endeavor to design quality product and that to with consistency in manufacturing process to deliver the intended performance of product.

5. PROPOSED WORK PLAN

1. Literature Survey: Literature survey will be done, available for listed single dose drugs and/or their combinations (regarding their physical and chemical properties, pharmacology and various analytical methods) shall be conducted. This forms the basis for the development of new HPLC and/ or HPTLC methods of analysis.

2. Procurement of Pure Drug Sample: Procurement of pure drug specimens draws utmost priority. The drugs will be obtained either buying from open market or as gift sample from respective companies / research laboratories of those brands.

3. Preliminary chromatographic experiments for assay method development for dosage form.

4. Defining Analytical Target Profile for assay method for dosage form.

5. Preliminary Risk Assessment for assay method based on literature and preliminary experimentation.

6. Optimization of chromatographic parameters using 'Design of Experiment' approach.

7. Validation of assay method as per ICH guidelines using following parameters

- ✓ Specificity
- ✓ Linearity
- ✓ Accuracy
- ✓ Precision
- ✓ Robustness
- ✓ Limit of Quantitation
- ✓ Limit of Detection
- ✓ Range

8. Application of the proposed method to marketed formulation.

9. Compilation of data, presentation and publication of research work in conferences and reputed journals.

10. Report writing and report submission

DURATION OF WORK

Present study is designed in such a way that it will come to a conclusive outcome within 03 years from the date of Allocation. The plan & duration of work is as follows.

Sr. No.	Work to be completed	Duration
1	Review of Literature	6 month
2	Procurement of drugs, chemicals and other requirements	6 month
3	Analytical method development for selected drug candidates using QbD approach	6 month
4	Validation of developed analytical method as per ICH guideline	6 month
5	Presentation and publication of research work in conferences and reputed journals	6 month
6	Report writing and report submission	6 month
	Total Duration of Project	**36 months**

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